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(54) Title: USE OF SUCRALFATE

(57) Abstract

Use of sucralfate for the preparation of a medicament for topical application to the skin or to any non-gastrointestinal, non-oral mucosal surface of an animal or a human, including the lining of body cavities, for the prophylaxis or treatment of any manifestation of inflammation or infection, for modification or facilitation of tissue regenerative processes, for the modulation of immune reactions, for the treatment or prophylaxis of non-bladder pre-malignant or malignant disorders, or for the prophylaxis or treatment of irritation, burns, or ulceration of the skin, connective tissue, or non-gastrointestinal, non-oral mucosa; or for the preparation of a medicament for topical application to the skin or any non-oral mucosal surface of an animal or a human for the treatment of laceration, lesions, or surgical wounds of the skin, connective tissue, or non-oral mucosa, or for the prophylaxis or treatment of skin, connective tissue, or non-oral mucosal aging. The medicament may be in the form of a powder, paste, ointment, lotion, gel, cream, salve, emulsion, suspension, solution, spray, sponge, strip, plaster, pad, dressing, or ostomy plate.

USE of SUCRALFATE

FIELD OF INVENTION

The present invention relates to the use of sucralfate as tissue regenerative, anti-allergic, antiinfective, antiviral, immunomodulating, antineoplastic and anti-inflammatory agent.

TECHNICAL BACKGROUND

While it is difficult to give an adequate description of inflammatory phenomena in terms of underlying cellular events in the injured tissue, there are certain features of the process that are generally agreed to be characteristic. These include fenestration of the microvasculature, leakage of the elements of blood into the interstitial spaces and migration of leukocytes into the inflamed tissue. On a macroscopic level, this is usually accompanied by the familiar clinical signs of erythema, oedema, tenderness and pain. During this complex response, chemical mediators such as histamine, serotonine, leucotrienes, prostaglandines, various chemotactic factors, bradykinin, lymphokines, kinin and complement system, lysosomal enzymes and cyclic nucleotides are liberated locally. Phagocytic cells migrate into the area, and cellular lysosomal membranes may be ruptured, releasing lytic enzymes. All these events contribute to the inflammatory response.

Several drugs are employed to suppress the manifestations of inflammation, including the adrenocorticosteroids, the large group comprising the so called non-steroid anti-inflammatory drugs or NSAIDs, and drugs such as immunosuppressive agents, chloroquine, penicillamine and gold salts.

NSAIDs are chemically a heterogeneous group of drugs, mainly constituting aromatic substituted carboxylic acids. Pharmacologically, they have anti-inflammatory, antipyretic and analgetic effects, and they inhibit prostaglandin synthesis and decrease thrombocyte aggregation. The mode of action of NSAIDs is not yet fully understood, although

it is known that they inhibit one or more of the mediator substances of inflammation. However, there is no good correlation between inhibition of prostaglandin synthesis and anti-inflammatory effect. The main indication for NSAIDs is rheumatic diseases, particularly where inflammatory processes in supporting tissues give rise to pain and joint-stiffness. Furthermore, the analgetic effects can be used as symptomatic pain relief in cases where the prostaglandin inhibitory effect can be utilized, such as dysmennorrhoea, urolithiasis, etc. Some of the drugs, including indomethacin, have also been used topically on the skin in the treatment of various dermatoses and as a topical anti-inflammatory agent in the eye.

The use of NSAIDs gives rise to a broad spectrum of side effects. Severe and often fatal blood dyscrasias are often seen, notably following the use of phenylbutazone, and gastrointestinal side effects are common with phenylbutazone, salicylates and indomethacin. Allergic reactions are common and may in some cases be due to prostaglandin inhibition with a resulting secondary increase in leucotriene levels. Hepatotoxicity and nephrotoxicity as well as side effects of the central nervous system are also common with these drugs.

Adrenocorticosteroids, and especially glucocorticoids, have potent anti-inflammatory effects when used in pharmacological doses. They specifically inhibit the early vascular phase of the inflammatory process by decreasing the vascular permeability and thereby granulocyt migration. Glucocorticoids also interfere with late inflammatory and reparative processes, in that they inhibit the proliferation of mesenchymale cells and the production of intercellulare macromolecules, including proteoglycanes and collagen. It has been shown experimentally that glucocorticoids inhibit, for example, macrophage function, production of humoral antibodies, cellular immunity, and possibly the release of lysosomal enzymes. The indications for systemic use of glucocorticoids are apart from substitution therapy very limited, because of side effects, and should be restricted to severe inflammatory rheumatic diseases, severe cases of allergic diseases such as asthma bronchiale and status asthmaticus and cases of haematological, renal, and gastrointestinal immunological disea-

ses. Topical use involves a much lower risk of side effects, and glucocorticoids are widely used for inhalation therapy in asthma, for topical application to the skin in nearly all cases of dermatosis and for injection in joints, bursae, tendons, etc., as well as for topical anti-inflammatory treatment of the eye, ear and nose. The most important side effects following topical use are skin and mucosal atrophy and acne, as well as microbial superinfections. In the eye, corneal ulceration, glaucoma and viral superinfections are feared and serious side effects, and steroids are in fact contraindicated in many cases.

Other anti-inflammatory drugs include penicillamine, chloroquine, gold salts and cytostatics. The main indication for these drugs is severe rheumatoid arthritis. The drugs are all given systemically, and they all exert a number of severe side effects.

Thus there would seem to be a need for alternative drugs to be used both topically and systemically to suppress or modify inflammatory reactions.

Sulphated saccharides, primarily sucralfate, have previously been indicated for the treatment of gastric and duodenal ulcers (cf. US 3,432,489; EP 161816; EP 192640) and for the treatment of emesis and diarrhoea in dogs and cats (cf. EP 133880). In radio-labelled form, sucralfate has also been used as a diagnostic agent for the imaging of gastrointestinal mucosa, since the substance binds selectively to ulcerated areas in the stomach and upper small intestine (cf. EP 107209).

The American Journal of Gastroenterology, 80(3), 1985, pp. 206-209; "Sucralfate: New Aspects in Therapy of Ulcers and Lesions" and the Second International Sucralfate Symposium Together With the World Congress of Gastroenterology in Stockholm, suggest the use of sucralfate for a variety of non-ulcer applications, including the treatment of stomatitis, post-sclerotic ulcer, reflux oesophagitis and bile reflux oesophagitis as well as for counteracting the ulcerogenic effects of aspirin.

SUMMARY OF THE INVENTION

It has surprisingly been found that sucralfate exerts an anti-inflammatory effect when applied topically to the skin and to mucosal surfaces, and that sucralfate exerts a beneficial effect on wounds when applied topically on epithelial surfaces outside the digestive tract.

Accordingly, in one aspect, the present invention relates to the use of sucralfate for the preparation of a medicament for topical application to the skin or to any non-gastrointestinal, non-oral mucosal surface of an animal or a human, including the lining of body cavities, for the prophylaxis or treatment of any manifestation of inflammation or infection, for modification or facilitation of tissue regenerative processes, for the modulation of immune reactions, for the treatment or prophylaxis of non-bladder pre-malignant or malignant disorders, or for the prophylaxis or treatment of irritation, burns, or ulceration of the skin, connective tissue, or non-gastrointestinal, non-oral mucosa; or for the preparation of a medicament for topical application to the skin or any non-oral mucosal surface of an animal or a human for the treatment of laceration, lesions, or surgical wounds of the skin, connective tissue, or non-oral mucosa, or for the prophylaxis or treatment of skin, connective tissue, or non-oral mucosal aging.

The measures generally taken in conventional skin care often do not suffice for the treatment of irritations and inflammations such as eczemas, rashes and burns caused by frequent contact of the skin with an irritant. In the case of burns, fast healing of the skin is desirable as the burn is otherwise liable to become infected. This may also be the case with ostomies, which often become inflamed and occasionally ulcerated due to, presumably, extensive contact with bodily secretions, since the ostomy appliances currently used are not completely liquid-tight and since moisture is often formed where they are sealed to the skin. Persistent ulcerations or inflammations may also cause moderate to severe pain, itching, soreness and other discomfort. In spite of intensive research conducted to solve the problems connected with the treatment of diseases of the skin and

mucosa and similar conditions as indicated above, no fully successful general therapy or prophylaxis has yet been devised.

The efficacy of sucralfate in effecting anti-inflammatory properties is surprising in view of the fact that the published literature only discloses sucralfate for use in the gastrointestinal tract, primarily for the treatment of peptic ulcers.

Furthermore, in European Patent Application 230023, concerning the use of sulphated saccharides for the enhancement of wound healing, it is stated that sucralfate gives rise to inflammatory reactions when applied to a wound. It is also stated that low levels of 0.1 to 1 mg/ml of the polysulphated saccharide is preferred in order to avoid local haemorrhage or inflammation at the wound site. In contradiction to this, excellent wound-healing and anti-inflammatory effects have been obtained according to the present invention, by using sucralfate topically on skin and mucosas.

In the same patent application (EP 230023), it is stated that the wound healing effects seen with sulphated saccharides are surprising, since sucralfate showed properties which make it undesirable for wound healing. It was concluded that wound healing with neovascularization and fibroblast (rather than macrophage) migration was not observed with sucralfate. In contradiction to this, we have observed an accelerated wound healing when sucralfate is applied topically to full-thickness skin wounds. In an animal study with small pigs, it was specifically observed that there was very little inflammatory reaction in the wound edge area (Example 8). In an *in vitro* model, the anti-inflammatory effect of sucralfate was studied. It was shown that an aqueous suspension of sucralfate exerted a dose-related inhibition of the PHA-activated production of the cytokines interferon gamma and interleukin 2 from human normal mononuclear cells, indicating an anti-inflammatory effect of sucralfate. It has been possible to demonstrate experimentally in animals that sucralfate exerts an anti-inflammatory effect which is comparable to that of indomethacin, when the drug is administered topically to the skin in order to protect against light-induced erythema (Example 10).

In human clinical studies (Example 9) a powder containing 50% sucralfate was used in the treatment of severe diaper rash in children with a short bowel following colectomy, and later the powder was used in the treatment of ulcerative skin inflammations around ileostomies. In all cases, the effect was dramatic and suggested a strong anti-inflammatory action of sucralfate. As the next step, a wound paste containing sucralfate was tested in the management of leg ulcers. Chronic ulcers of both arteriosclerotic and venous stasis etiology were selected for the study. Approximately half of the patients showed marked wound-healing. However, the most glaring effect was the pain relief spontaneously reported by all the patients, and the decrease in tissue oedema and in skin inflammatory reactions seen in the wound surroundings.

This observation of a conceivable anti-inflammatory effect of sucralfate led to the testing of the drug administered topically as a cream or an ointment to various types of dermatoses. A marked clinical effect was seen in the management of atopic dermatitis, psoriasis and toxic hand eczema. The results suggest that sucralfate exerts an anti-inflammatory effect which is at least comparable to that of corticosteroids, in the management of steroid responding skin diseases (Example 9).

The unique combination of anti-inflammatory activity with that of a wound-healing or tissue stimulating effect, (as opposed to hitherto known anti-inflammatory drugs, such as the steroids and NSAIDs) makes sucralfate an interesting compound to be used as an alternative to conventional anti-inflammatory drugs. Furthermore, sucralfate's extremely high tolerability, as documented by the total absence of side-effects following its use in the treatment of peptic ulcer, and the very high tolerability of sucralfate when used topically on the skin and mucosa makes sucralfate very attractive as an alternative to conventional anti-inflammatory drugs.

It is furthermore contemplated that sucralfate modifies or inhibits inflammatory reactions and/or stimulate tissue regenerative processes via other, not yet fully understood mechanisms.

It has been observed that sucralfate, when used internally in the treatment of peptic ulcers, binds preferentially to the surface of the ulcer. It is currently believed that this is a property common to sulphated saccharides, and that this binding is the result of an ability of sulphated saccharides to bind to proteoglycanes and hyaluronic acid. These structures are components of the surface of many cells, and they protect and stabilize the cell so the exterior cell surface remains intact. In other cases, e.g. in dermis and supportive tissue, proteoglycanes and hyaluronic acid form a protective matrix in which cells are embedded. Furthermore, it is known that certain sulphated saccharides, e.g. heparan sulphate, dextran sulphate and xylose sulphate, are hyaluronidase inhibitors.

Hyaluronidases are enzymes which catalytically cleave the glycosidic bonds of hyaluronic acid and glycosaminoglycanes. The decomposition of hyaluronic acid and glycosaminoglycanes by hyaluronidases therefore leads to exposure of the cells, via destruction of the cell surface or the supportive matrix substance, as well as to damage from various agents such as pathogens, inflammatory mediator substances, inflammatory agents and corrosive agents. Thus it is believed that by inhibiting hyaluronidases, sulphated saccharides promote the regeneration of the cell surface and the protective connective tissue matrix, and thereby effect an anti-inflammatory and tissue regenerative action.

Decomposition products of hyaluronic acid and glycosaminoglycanes may also act as mediator substances of inflammation themselves, and via inhibition or modification of such decomposition, sucralfate may inhibit or modify inflammatory reactions and facilitate and modify tissue regeneration.

Thus it is contemplated that the above-mentioned pharmacological effects of sucralfate result in a "strengthening" of epithelial and mucosal linings. Apart from effecting an anti-inflammatory action, this strengthening of the exterior cell surface and connective tissue cell matrix will also make it more difficult for bacteria and virus to penetrate and colonize the cells and the tissue. Instead of a direct antimicrobial effect, an indirect effect will thus be obtai-

ned by applying sucralfate to mucosal and epithelial surfaces. Thus sucralfate may be used topically in the treatment of bacterial, viral or mycotic infections of skin and mucosa. The antimicrobial effect may possibly also be utilized by applying sucralfate directly to supportive tissues in connection with surgery. Many infections spread in the tissue by means of hyaluronidases produced or induced by the pathogens themselves. It is contemplated that the hyaluronidase inhibiting effect of sucralfate prevents the spreading of such infections.

Such anti-inflammatory and anti-infective actions may furthermore be utilized when implanting or inserting medicotechnical devices into the body. By incorporating sucralfate into the surface coating of a device or into the material of the device itself, it is contemplated that infections and inflammatory tissue reactions, including thrombophlebitic reactions, around the device can be diminished (see Example 13). Examples of devices where such a technique could be used are urethral catheters, peritoneal dialysis catheters, e.g. dural and spinal catheters, venous and arterial catheters, electrodes, breast protheses, pacemakers, middle ear tubes, eye lenses, vascular prostheses, hip prostheses, etc. Other uses may comprise coating of any material to be placed directly on the skin or mucosa for longer periods, such as ostomy plates, external prostheses, etc.

It is furthermore contemplated that the "strengthening/modifying" effect of sucralfate on the cell surface may be utilized in the management of malignant disorders. Examples are treatment of superficial skin and mucosal malignancies such as basal cell carcinomas, cervical dysplasia and carcinoma, etc. by topical application of sucralfate or another sulphated saccharide on the lesions, and possibly also by placing depot preparations which release sucralfate into the surrounding tissue in connection with surgery for malignant diseases. It is furthermore contemplated that sucralfate might be useful as an addition to cell cultures *in vitro* because of its cell surface modifying action.

The present invention further relates to a pharmaceutical preparation, in particular for any of the uses stated above, which comprises

sucralfate alone or together with a pharmaceutically acceptable excipient. The invention relates additionally to a topical preparation for the prophylaxis or treatment of laceration or lesions of skin, the preparation comprising sucralfate together with a pharmaceutically acceptable carrier or excipient.

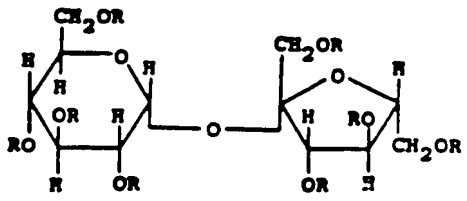
In a still further aspect, the invention relates to a method for preventing or treating any manifestation of inflammation or infection of the skin or any non-gastrointestinal, non-oral mucosal surface of an animal or a human, including the lining of body cavities; for modifying or facilitating tissue regenerative processes; for modulating immune reactions; for preventing or treating non-bladder premalignant or malignant disorders; for preventing or treating irritation, burns, or ulceration of the skin, connective tissue, or non-gastrointestinal, non-oral mucosa; for the treatment of laceration, lesions, or surgical wounds of the skin, connective tissue, or non-oral mucosa; or for preventing or treating skin, connective tissue, or mucosal aging, the method comprising applying to the skin, mucosa or tissue a therapeutically or prophylactically effective amount of sucralfate.

Interesting embodiments of the use, the preparation, and the method of the invention appear from the appended claims.

DETAILED DISCLOSURE OF THE INVENTION

In certain cases, it may be an advantage to use the sucralfate in combination with another wound-healing substance such as a non-sulphated polysaccharide, for instance hyaluronic acid, *vide* Example 7.

Sucralfate may be represented by the following formula:



R = $SO_3[Al_2(OH)_5]$

The substance may, for instance, be prepared as disclosed in US 3,432,489 by reacting a 1-10% aqueous solution of sucrose octasulphate or an alkali metal or alkaline earth metal salt thereof with a 1-10% aqueous solution containing aluminium ions, preferably $AlCl(OH)_2$ at room temperature and a pH of 4-4.5. The sucrose octasulphate may be prepared by reacting sucrose with $ClSO_3H$, H_2SO_4 or H_2SO_4-C_5H_5N.

Sucralfate may also be termed sucrose octakis(hydrogen sulphate) aluminium complex. Its CAS number is 54182-58-0. The commercial product is a white powder which is practically insoluble in water and most organic solvents; it is soluble in acids and alkalis. In practice, there may be slight variations in the chemical composition, e.g., due to the fact that the sulphation may be slightly incomplete so that the product may, e.g., contain a certain proportion of molecules which are not octasulphated (persulphated), but rather less sulphated such as heptasulphated. Such minor variations in the commercial product are well known and are reflected in the fact that e.g., the aluminium content in commercial products may range from 17 to 21% and sulphur from 9.5 to 12.5%. In the present context, the term "sucralfate" also comprises such generally accepted minor variations. Although there may be cases where the sucralfate may be administered as such, it will typically be compounded with one or more pharmaceutically acceptable carriers or excipients to present it in a form which is suitable for topical application. In other words, it will be in the form of a liquid, semi-solid or solid topical preparation such as a powder, paste, ointment, lotion, gel, cream, salve, emulsion, solution, suspension, spray, sponge, strip, plaster, pad, dressing or ostomy plate.

For topical application, the preparation may be formulated in accordance with conventional pharmaceutical practice with pharmaceutical excipients conventionally used for topical applications such as pectin, gelatin and derivatives thereof, polylactic acid or polyglycolic acid polymers or copolymers thereof, cellulose derivatives such as methyl cellulose, carboxymethyl cellulose or oxidised cellulose, guar gum, acacia gum, karaya gum, tragacanth gum, bentonite, agar,

carbomer, bladderwrack, ceratonia, dextran and derivatives thereof, ghatti gum, hectorite, ispaghula husk, polyvinylpyrrolidone, silica and derivatives thereof, xanthan gum, kaolin, talc, starch and derivatives thereof, paraffin, water, vegetable and animal oils, polyethylene, polyethylene oxide, polyethylene glycol, polypropylene glycol, glycerol, ethanol, propanol, propylene glycol, (glycols, alcohols), fixed oils, sodium, potassium, aluminium, magnesium or calcium salts (such as the chloride, carbonate, bicarbonate, citrate, gluconate, lactate, acetate, gluceptate or tartrate).

The preparation of the invention may also contain other additives such as emulsifiers, stabilizing agents, preservatives, etc.

Plasters, sponges, strips, pads or other dressings may be prepared by impregnating a dressing material such as cotton wool or gauze or a polymeric substance with suspension of sucralfate followed by drying. Alternatively, a paste, lotion, cream or gel containing the sucralfate may be spread over the dressing material, conveniently immediately prior to use.

A suitable starting material for the preparation of an ointment, paste, lotion, cream, suspension, or gel is a micronized suspension of sucralfate in polyethylene glycol. By means of a 3-roll mill, the sucralfate powder is ground together with a liquid polyethylene glycol, e.g., PEG 400, and the resulting preparation contains up to 60-75% by weight of sucralfate particles with a fairly uniform particle size of about 5-10 μm or less, evenly suspended in the polyethylene glycol. Suitable polyethylene glycols are in the range of mw 200-6000. Such a paste can then be further suspended in any suitable pharmaceutical preparation using well-known pharmaceutical methods.

For the treatment of mucosa, e.g. the vaginal, nasal and ocular mucosa, the preparation of the invention may for instance be formulated in the form of a vaginal suppository, a nasal drop or insert or eye drops or eye salve. Such formulations may be prepared in accordance with conventional pharmaceutical practice using conventional excipients such as some of those mentioned above.

The pharmaceutical preparation of the invention generally comprises the sucralfate in an amount of 0.001-99%, typically 0.01-75%, more typically 0.1-20%, especially 1-10% by weight of the total preparation. In particular, when the sulphated saccharide is sucralfate, a preferred concentration thereof in the preparation is often 0.5-50%, especially 0.5-25%, such as 1-10%. It is suitably applied 1-10 times a day, dependent on the type and severity of the condition to be treated.

The concentration of the sucralfate to be used in each particular case will of course depend upon the type of preparation and the intended use, but also on the particle size and shape thereof; the smaller the particle size, the faster will be the distribution of the sucralfate. Sucralfate is often preferably used in the form of a fine powder, for example having a particle size of 200 μm or less, such as 100 μm or less. Examples of very small particle sizes which may be desirable for certain purposes are e.g. 50 μm or less, such as 20 μm or less, in certain cases 10 μm or less, such as 5 μm or less.

The preparation may contain other active agents than the sucralfate, such as antibacterial agents, antiviral agents, antimycotic agents, antiparasitic agents, sun protective agents, vitamins and vitamin derivatives or analogues, antineoplastic agents, antifibrinolytic agents, blood coagulation modifying agents, antiseptic agents, analgesics, topical anesthetics or anti-inflammatory agents.

As mentioned above, the sucralfate is indicated for use in connection with any skin, mucosa or tissue condition involving irritation, inflammation or burns, or for the prevention of ulceration of the skin. Furthermore, it has been found particularly advantageous to treat skin conditions caused by contact with an external chemical agent (e.g. ar allergen or an irritant or a corrosive substance such as an acid or a base) or with body secretions such as urine, sweat or gastrointestinal secretions, or by external pressure, or by heat, or ionizing radiation, or light (which in the present specification and claims includes ultraviolet light) by means of the sucralfate, or to add the sucralfate as a prophylactic measure to prevent skin damages resulting from these agents or secretions.

Examples of particular conditions for which use of sucralfate is therapeutically or prophylactically indicated include:

Skin diseases, (including lips, vaginal mucosa and perianal areas), such as:

Miliaria, defined as an acute inflammatory pruritic eruption resulting from obstructed sweat glands, often precipitated by even minor skin irritation, e.g. application of adhesive plasters or excessive moist heat (sunburn, diaper, exercise).

Intertrigo, defined as acute superficial inflammation of opposing skin surfaces, characterized by erythema, abrasion, maceration, and, in some cases, superficial fissuring.

Pruritus, defined as a generalized or localized itching sensation, which the patient instinctively attempts to relieve by scratching.

Acne and rosacea, defined as inflammation of the sebaceous glands and characterized by seborrhoea comedones, pustules, papules and nodules.

Superficial bacterial skin infections such as erythrasma; superficial fungal infections such as ringworm and candida; viral infections such as herpes simplex, herpes zoster, measles, varicella, warts, Condyloma acuminata; vaginosis, either nonspecific or caused by mycoplasma, chlamydia, candida, *Thrichomonas*, etc.

Dermatitis, defined as an acute or chronic superficial inflammation of the skin, whether microbially infected or not, characterized by erythema, oozing, crusting, scaling, and sometimes by vesicles. Included are contact dermatitis, atopic dermatitis, seborrhoeic dermatitis, neurodermatitis, lichen simplex, drug eruption, erythema nodosum, erythema multiforme, pityriasis

rosacea, lichen planus, psoriasis, ichthyosis, stasis dermatitis and chronic dermatitis of the hands and feet.

Acute sunburn and other superficial burns, and protective against sunburn.

Skin irritation secondary to the presence directly on the skin of a prosthetic device, diaper, ostomy pad or similar, bandage, plaster, electrode, catheter, etc.

Prophylactically against pressure sores.

Boils, furuncles, carbuncles, hidrosadenitis and fistules.

Hemorrhoides, perianal pruritus and vulvitis.

Cosmetically against wrinkles and aging skin, both as active and prophylactic treatment, and against dandruff.

Respiratory diseases such as:

Allergic rhinitis, characterized by seasonal or perennial sneezing, rhinorrhea, nasal congestion, and often conjunctivitis and pharyngitis.

Acute rhinitis, characterized by oedema of the nasal mucosa, nasal discharge and obstruction. In most cases caused by a common virus.

Pulmonary diseases, such as intrinsic or extrinsic asthma bronchiale, pulmonal inflammatory reactions secondary to chronic bronchitis, pneumoconioses, pulmonary fibrosis, Goodpasture's syndrome, etc.

Ear, nose and throat disorders such as:

Acute external otitis, furunculosis and otomycosis of the external ear.

Traumatic and infectious myringitis.

Acute eustachian salpingitis.

Acute serous otitis media.

Acute and chronic sinusitis.

Eye diseases such as:

Oedema in the eye region caused by trauma or foreign bodies, or postoperative inflammation.

Eyelid allergies and blepharitis; hordeolum and chalazion.

Acute and chronic catarrhal conjunctivitis of any microbial etiology

Allergic (vernal) conjunctivitis.

Trachoma.

Scleritis, episcleritis.

Superficial punctate keratitis, dendritic (herpetic) keratitis, disciform keratitis and corneal wounds.

Iritis, iridocyclitis.

Malignant and premalignant disorders such as basal cell carcinoma, cancer in situ colli uteri.

The invention is further illustrated by the following non-limiting examples.

EXAMPLE 1

A topical powder preparation was prepared from the following ingredients:

Sucralfate*	30 g
Pectin	10 g
Gelatin	10 g
Carboxymethylcellulose	10 g

* Provided by Abic Laboratories, Israel, in finely divided form.

The finely divided sucralfate (particle size 2-100 μm) was thoroughly mixed with the other ingredients in finely divided form (particle size <250 μm) to produce a powder.

EXAMPLE 2

A topical ointment preparation was prepared from the following ingredients:

Sucralfate	30 g
Pectin	10 g
Gelatin	10 g
Carboxymethylcellulose	10 g
Fractionated coconut oil	60 g

The finely divided sucralfate (particle size 2-100 μm) was thoroughly mixed with the other ingredients in finely divided form. The fractionated coconut oil was added to the resulting powder to a suitable consistency and a substantially homogeneous dispersion of the particulate components.

EXAMPLE 3

A topical ointment preparation was prepared from the following ingredients:

Sucralfate	30 g
Hyaluronic acid	0.6 g
Pectin	10 g
Gelatin	10 g
CMC	10 g
Fractionated coconut oil	60 g

The finely divided sucralfate (particle size 2-100 µm) was thoroughly mixed with the other ingredients in finely divided form. The fractionated coconut oil was added to the resulting powder to a suitable consistency and a substantially homogeneous dispersion of the particulate components.

EXAMPLE 4

A topical eye preparation was prepared from the following ingredients:

Sucralfate *	2 %
Carbopol 934	0.5 %
Mannitol	5 %
Benzalkoniumchloride	0.01 %
Sodium EDTA	0.05 %
Sodium hydroxide q.s	ad pH 6
Sterile water	ad 100 %

* Micronized sucralfate (particle size 10 µm), provided by Guilini Chemie, W. Germany.

EXAMPLE 5

Eye preparation

An eye preparation was prepared from the following ingredients:

Sucralfate*	2%
Propyl methyl cellulose	0.35%
Benzalkonium chloride	0.01%
Sodium EDTA	0.05%
Sodium chloride	0.8
Sterile water	q.s.

* Micronized (10 μm), provided by Guilini Chemie Ludwigshafen, W. Germany.

EXAMPLE 6

A topical preparation for skin and mucosa was prepared by mixing 5% by weight of a sucralfate powder (particle size 50-100 μm, provided by Guilini Chemie, W. Germany) with a mixture of cetanole, adeps lanae purificatae, isopropyl myristas, Tween 60, Span 60, dimeticone, glycerol, sorbic acid and sterile water.

EXAMPLE 7

A) A topical preparation for mucosa and skin was prepared from the following ingredients:

Sucralfate powder *	5 %
Paraffin oils, glycerine, cetyl alcohol	55 %
Quarternary ammonium compounds	0.7 %
Stearyl alcohol	3 %
Eucalyptus oil	q.a.

B) A topical eye drop as a watery suspension was prepared containing:

Sucralfate *	2 %
Oxypropylmethylcellulose 4000	0.35%
(preserved with Phenylhydragyri-nitras)	

* Micronized sucralfate (≤10 µm), provided by Guilini Chemie, W. Germany.

EXAMPLE 8

Wound-healing effect of sucralfate in an animal study

The present example illustrates the wound-healing effect of sucralfate and also the surprising anti-inflammatory effect of sucralfate.

Two crossbred SPF pigs (Danish landrace x Yorkshire LYY, body weight 25-30 kg) from Ellegaard Forsøgsgrise, Sorø Landevej 302, DK-4261 Dalmose, were used in the test.

Twice daily, the pigs were offered a standard granulated pig diet, ØA Baconblanding 20, from Østsjællands Andel a.m.b.a. At week-ends they were only fed once but received double ration. At each feeding time they were given tap water at libitum.

The pigs were housed separately in wire mesh metal cages.

The room temperature was set at 19°C and the relative humidity at 55%. The light was on from 06 to 18 h.

Test substance

The test substance (sucralfate) was administered as the ointment described in Example 3. The control was treated with DuoDerm ™(a commercial product by ConvaTec, USA).

Wounding procedure

The pigs were anaesthetized with Sedaperone® (i.m.) and Hypnodil® (i.p.). Atropin (i.m.) was administered at the same time to prevent salivation. The hair of the back was clipped with an electric clipper before washing with soap and water followed by disinfection with 70% ethanol. Before surgery the skin of the back was rinsed with sterile 0.9% saline.

The wounds were prepared surgically using a scalpel and a template with an area of 12 x 25 mm.

After incision through the entire cutis (epidermis and corium), the skin of this area was removed by gentle cutting of subcutaneous tissue as closely to the corium as practically possible. The number of wounds on each pig was 4 on each side.

Treatment

Immediately after wounding, half the wounds were treated with the ointment, while the rest of the wounds were treated with DuoDerm™ as controls. Test wounds were treated with the ointment and covered with Tegaderm and control wounds were treated with DuoDerm adhering dressings providing an occlusive dressing. The dressings were covered with gauze packs fixed with Scanport tape.

During the entire study period the pigs wore nylon mesh jackets in order to prevent dislodgement of the wound dressing.

On days 2, 4, 6, 8 and 10 after wounding the pigs were sedated and subsequently dosed. The dressing was removed and each wound was rinsed with dry gauze packets. On days 0, 2, 4, 6, 8, 10 and 12 a transparent sterilized plastic film was applied to the skin for drawing lines of the wound area. As soon as re-epithelialization took place, lines were drawn both at the edge of the wound and at the edge of the re-epithelialization zone.

Before dosing the wounds were photographed. After dosing the wounds were covered as described above.

Histopathology

On day 8 a fine needle biopsy was taken from the center of all wounds. The biopsies were fixed in 4% buffered formaldehyde for microscopy.

On day 12, the pigs were sacrificed while anaesthetized by exsanguination after cutting the subclavian artery. The wounds were excised and fixed to a piece of cardboard paper in order to prevent shrinkage during fixation in 4% buffered formaldehyde solution.

Paraffin sections of biopsies and wounds were stained with haematoxylin and eosin for microscopic examination.

The microscopic examination at 4 x 10 times magnification included semiquantitative quantification of the area of the wound surface which was not covered with epithelium.

Determination of wound area

The plastic films were photocopied at 40% magnification. Each wound area was quantified by weighing the photocopy paper wound area after excision with a pair of scissors.

The results are shown in Tables 1 and 2.

Table 1

Area of wounds in pig No. U-1

Day after wounding	% of day 0 wounds		Test substance wounds in % of control
	Control	Test substance	
0	100	100	87.6
2	108.1	102.0	82.6
4	151.0	116.8	89.0
6	78.4	72.0	80.4
8 e.l.	18.6	26.6	125.3
8 w.e.	58.5	45.4	67.9
10 e.l.	6.8	13.4	171.9
10 w.e.	56.4	41.2	64.0
12 e.l.	5.8	6.1	92.6
12 w.e.	49.9	28.5	52.2

n = 4

e.l. = area within epithelial line
w.e. = area within wound edge.

Table 2

Area of wounds in pig No. U-2

Day after wounding	% of day 0 wounds		Test substance wounds in % of control
	Control	Test substance	
0	100	100	96.8
2	111.2	111.6	97.1
4	123.7	116.5	91.1
6	98.5	90.2	88.6
8 e.l.	30.0	24.9	80.6
8 w.e.	78.0	57.2	71.0
10 e.l.	22.8	12.0	50.9
10 w.e.	62.7	52.1	80.4
12 e.l.	12.5	1.8	13.8
12 w.e.	54.4	38.3	66.9

n = 4

e.l. = area within epithelial line
w.e. = area within wound edge.

In the wounds which had been treated with the test substance, a marked anti-inflammatory effect of the test substance was noted at the wound edge and the surrounding tissue, as compared to wounds treated with the control.....

EXAMPLE 9

Human Clinical Trials

A) Two babies (a boy and a girl) who had been operated to correct congenital megacolon (Hirschsprung's disease) developed a severe rash with erythema, inflammation and pustules (presumed to be caused by contact with digestive enzymes and possibly acid due to the shortening of the intestines). The preparation of Example 1 was applied to the affected skin at each change of diapers. After one day of treatment the condition had improved dramatically, and the rash disappeared completely after two to three days of treatment. The treatment was continued for six months. For the first four months after the operation, interruptions in the daily application of the sucralfate-containing powder resulted in recurrence of the rash. After six months, however, it was possible to discontinue the treatment with occasional resumption after, for instance, diarrhea.

B) Ten oncological patients with ileostomies who had developed ulcerations around the ileostomies were treated with the preparation of Example 1. A control group of ten other patients who had similarly developed ulcerations around ileostomies were treated with a powder preparation containing equal amounts of pectin, gelatin and carboxymethylcellulose (i.e. the preparation of Example 1 without any sucralfate). In each case, the powder was applied at each change of the ostomy bag for two weeks.

After three days of treatment none of the patients in the group treated with the sucralfate-containing powder showed any ulceration around the ileostomy, whereas 7 of the patients in the control group did to greater or lesser extent. After two weeks of treatment one of the patients in the group treated with the sucralfate-containing powder had had ulcerations for two periods each lasting three days, one of the patients had died, and the others were free from ulceration for the entire period. In the control group, two patients were free from ulceration at all times, whereas all the others had ulcerations/severe irritation lasting two days or more. Two of the patients had ulcerations around the ileostomy for the entire period.

Based on these trials it was concluded that the preparation of the invention may successfully be used in the treatment of ulcerations and similar conditions of the skin caused by gastrointestinal secretions. Trial B) shows that sucralfate is responsible for the improvement rather than any other ingredient in the composition.

C) Fourteen elderly patients (aged 49-86 years, mean 70), with chronic leg ulcers of either ischaemic or venous stasis etiology, were treated with the preparation of Example 2. At the start of the therapy, surgical debridement was made. The wounds were then filled up with the paste, and according to the nature of the surrounding skin, the wound area was covered with either a plastic film or with parchment paper. At the weekly changes, surplus paste was carefully removed so as not to destroy granulation tissue, if present, and the treatment was repeated, i.e. the wound was filled with new paste and the wound area covered. In seven patients, there was a complete or nearly complete wound healing after two to three months of therapy. The wound-healing effect was evaluated by measuring the size of the wound at each control. During the first month of therapy, there was a reduction in the size of the wound in nine cases, the initial wound size being reduced by an average of 76% in the nine cases. In three cases there was no effect on wound size, and in the last two cases this measurement was not made. Pain in the wound was assessed on a scale from 0 = absent to 3 = severe. In all cases there was a marked pain relief, typically within a few hours after application of the wound paste. It was observed that the oedema in the surrounding tissue decreased and that the macerated and inflamed skin in the wound surroundings healed. Most of the wounds had fibrin, pus, and yellow necrosis at the start. They had in all cases turned into "red wounds" after treatment, with clean red granulation tissue free of infection. The mean scores for pain and eschar at baseline and during the following four weeks of treatment are shown in Table 3:

Table 3

	Mean score (0 = absent to 3 =severe)				
	Baseline	Week 1	Week 2	Week 3	Week 4
Pain:	2.21	1.50	1.31	1.18	1.00
Eschar:	1.92	1.38	1.19	0.67	0.60

It would seem that sucralfate used topically on chronic leg ulcers exerts a definite wound-healing effect. At the same time, there was a marked anti-inflammatory effect of the sucralfate wound paste, in that oedema in the tissue decreased and inflammated and macerated skin around the wound healed.

D) The anti-inflammatory effect of sucralfate on various types of dermatosis was evaluated in adult patients with atopic dermatitis, psoriasis, toxic hand eczema and folliculitis. The preparation comprised 5% by weight of sucralfate powder mixed in a fatty vehicle containing herbal extracts of chamomile (6%) and arnica (4%). The ointment was applied morning and evening. Table 4 summarizes the demographic data and diagnostics of treatment of the patients included in the study.

Table 4

Diagnosis	No. of Patients	Sex	Age	Drug tested for
Atopic dermatitis	8	F	18-44	1-8 months
Atopic dermatitis	6	M	21-33	1-5 months
Psoriasis (universal)	3	M	33-39	1-4 months
Psoriasis (universal)	5	F	19-28	3-8 months
Psoriasis (local)	6	M	19-31	1-6 months
Psoriasis (local)	7	F	23-33	1-8 months
Toxic hand eczema	5	F	35-48	5-8 months
Folliculitis (beard)	7	M	30-60	2-3 months
Anal-vulval pruritus	4	F	48-71	4 months

Topical application of sucralfate ointment twice daily resulted in improvement or complete cure in all 51 cases. All of the patients except two females with local psoriasis and the seven males with beard folliculitis had previously received extensive topical treatment with steroids. The patients with atopic dermatitis had disease histories of 10-20 years, and they all suffered from rebound phenomena following use of steroids. There was a marked improvement after 10 days of treatment with sucralfate ointment, and 10 out of the 14 patients with atopic dermatitis have been cured in the sense that the patients have been completely free of dermatotic symptoms during treatment periods of up to 8 months. Patients with psoriasis have shown improvement after 2 to 4 weeks of treatment, and the improvement has in all cases been maintained for the entire treatment period. Patients with toxic hand eczema have shown improvement after one week, and the patients have been completely cured in three cases. A good effect has been shown with beard folliculitis over a treatment period of 2 to 3 months, and females with vulvovaginitis symptoms were freed of their pruritus. No side effects have been seen during treatment with sucralfate ointment covering a total period of 156 patient months.

In an few clinical cases, a marked antimicrobial effect has been observed with topical application of sucralfate to skin and mucosas:

E) Two patients with a superficial fungal skin infection (ringworm), received the sucralfate preparation of Example 6. After one day there was a marked improvement, and after three days of application of the sucralfate preparation two times a day, the skin was completely free of clinical signs of any fungal infections.

F) Two females with severe and long standing non-specific colpitis of suspected infectious etiology received the sucralfate preparation of Example 6. The ointment was applied twice a day to the vaginal mucosa. In both cases there was a complete clinical cure after two weeks of therapy. Both patients had received almost every kind of topical therapy, including steroids and antimicrobials, without effect for several years.

G) The sucralfate ointment of Example 7 has been used topically on herpes labialis. The ointment was applied three to six times daily, and the treatment was started as soon as possible after the herpetic eruption. Four young females have been evaluated, and in all four cases treatment has been successful in the sense that pain was reduced and there was a reduction in eruption of blisters. The skin was completely healed within two to four days after the start of treatment.

H) The sucralfate ointment of Example 7 was tested in the treatment of acne vulgaris. Three females aged 16-20 years applied the ointment topically morning and evening. There was a marked reduction in the inflammatory reaction of the skin after one day of treatment, and after one week there was a reduction in the number of follicles. All three patients had previously tried many kinds of anti-acne therapy, including vitamin A and systemic antibiotics. Sucralfate resulted in a more lasting effect, and there have been no rebound phenomena during treatment periods of up to 3 months.

I) The sucralfate ointment described in Example 9 D) was tested on facial wrinkles around the eyes. Five females aged 38-45 have used the ointment twice daily, and a beneficial effect has been reported after 1-2 weeks of treatment.

EXAMPLE 10

Ultraviolet sunburn (erythema) study in guinea pigs:

Twelve young adult SPF albino guinea pigs (male and female, 10 weeks of age, body weight 350-400 g) of the Dunkin Hartley strain, from Moellegaard Breeding Centre Ltd., were divided into a positive test group (8 animals) and a vehicle control test group (4 animals).

The animals were housed in opaque PPL (type IV) cages, two or three to a cage, males and females separated. They had free access to a pellet diet, "3113 Altromin", and vitamin C enriched tap water. The room temperature was set at 21°C ± 2°C and the relative humidity at 55% ± 15%. The air was changed 6 times an hour, and the light was on from 06 to 18 h. The acclimatization period was one week.

The control substance was Indomethacin 10%, and the test substance was sucralfate 5%, both in a vehicle of paraffin oil, Ph.N.

The day before treatment, both flanks of the animals were clipped free of hair and shaved with an electric razor. The next day, the unaneasthetized animals were restrained on the side opposite that which was to be exposed to the light. A rubber sheet with two openings with a diameter of 4 cm (each about 12.5 cm^2), was placed on the clipped and shaved flank of each animal and the rest of the body was covered in order to protect the animal from the UV-light, except for the two treatment sites. Two guinea pigs at a time were subsequently exposed to light from ultraviolet lamps (T1 20/12, UVB, Philips), at a distance of 6 cm for 20 minutes.

In the center of the two erythema treatment sites (each about 5 cm^2), 0.05 ml of the test substance, the control substance or the vehicle, respectively, was applied. After application, the substance was massaged into the skin for a period of about 30 sec. with the tip of the finger. To measure prophylactic effectiveness, the application took place 30 minutes before the UV-exposure.

Each of the 16 flanks of the 8 animals in the positive test group were treated with both the 5% sucralfate test substance and with the 10% indomethacin as the positive control substance. In half the animals the anterior treatment site was treated with the test substance and the posterior site were treated with the positive control substance and vice versa. In the 4 animals of the vehicle control group, the procedure was the same as above, except that the positive control was replaced with paraffin oil.

Two, four, six and twenty-four hours after termination of the UV-light exposure, the treatment sites were read and evaluated according to the following scale:

Erythema (ER) reduction	Score
No visible sign of ER	0
Barely discernible ER	1
Faint non-confluent ER	2
Marked non-confluent ER	3
Marked non-confluent or confluent zones of ER beyond application area	4
Homogeneous ER	5
Homogeneous ER beyond application area	6

The animals were read blindly, and the erythema reduction scores for each substance were averaged. The vehicle control average has been substracted from the positive control average and test substance average, respectively, to yield the net erythema reduction activity.

The following erythema reduction activity was found:

Indomethacin 10% in paraffin oil: 72% prophylactically

Sucralfate 5% in paraffin oil: 68% prophylactically

It can be concluded that sucralfate exerts the same protection as indomethacin against the development of light-induced erythema, when

applied topically to the skin of guinea pigs 2 hours before UV-exposure.

EXAMPLE 11

Sucralfate eye and nose drops in dogs and cats

The preparation of Example 7 B) was evaluated in 20 dogs with chronic red eyes presumably due to infections and allergic reactions. The eye drops were applied to fornix inferior morning and evening. Fourteen out of twenty animals responded to the treatment, 5 of which had failed to respond to previous treatment with topical eye antibiotics including chloramphenicol and fusidine. The effect was seen after 1-5 days and the treatment period was in most cases 2-3 weeks. The same preparation was used in the treatment of chronic congestion of the tear canals of purebred cats. Ten cats were investigated, and in all ten cases there was a complete cure with cessation of tear flooding within 2-3 days of treatment. The effect of the treatment was at least as good as that obtained with steroid therapy. Finally, the same preparation was used as nasal drops for three cats with chronic recurrent upper air passage infections. One drop was applied to the nostrils morning and evening, and no other treatment was given. In all three cases the cats were completely free of symptoms of air passage infection after 2-3 days of treatment.

EXAMPLE 12

Rabbit eye tolerance test of sucralfate eye drops

The primary eye irritative effect of the sucralfate eye drops of Example 7 B) was tested in rabbits. The testing was done on four SPF albino female rabbits. Only the left eye was treated and the right eye served as an untreated control. About 0.1 ml of the test preparation was applied to the eye by gently pulling the lower eyelid away from the eyeball to form a cup into which the test substance was placed. The lids were then gently held together for about one second.

The eyes were examined and the grade of occular reaction was recorded 1 hour later. 24 hours later an examination was performed before and after instillation of ocoluguttae fluoresceini. After the examination the eyes were rinsed with 20 ml of a 0.9% sodium chloride solution. The eyes were also examined 48 and 72 hours after treatment. Cornea, iris and conjunctiva (including discharge) were inspected, and any reactions and changes were observed and scored. Slight discharge of conjunctiva was observed in two of the rabbits at the first examination. No reactions of conjunctiva, iris, or cornea were observed in any of the rabbits at the 24, 48 and 72 hour examinations.

Mean score values, as determined by a variety of different standard criteria, for cornea opacity, iris lesion, redness of conjunctiva and oedema of conjunctiva (chemosis) were all 0.0.

According to the criteria in the Official Journal of the European Communities, L 257, 1983, the directive of the commission, 83/467/EEC of July 29, 1983, and the above mean values, it must be concluded that the tested sucralfate in a 2% aqueous suspension shall not be classified an eye irritant.

EXAMPLE 13

Prevention of thrombus formation with a central vein catheter with a sucralfate coating

Thrombus formation due to a central vein silicone catheter was investigated with and without a sucralfate coating in a guinea pig model. The local tissue reaction to such catheters implanted in muscle tissue was also studied. Eight silicone catheters (7 French Silicone from Durascau Medical Products A/S, Odense) were used. Each catheter had a length of about 15 cm. Four catheters were coated by a dip-coating technique with a microcrystalline suspension of sucralfate (40% w/w), and the catheters were sterilized by radiation.

Silicone catheters (2 mm) were inserted surgically in the jugular vein, until the tip reached the level of the bijugular junction. The

outer end of the catheter was bent and fixed to the muscle tissue close to the vein. The skin was closed according to routine procedures. Two other catheters were inserted transversely in the lumbar part of the longissimus dorsi muscle. Each catheter was inserted via a small medial skin wound and led out through another small skin wound, and then subcutaneously tunnelled back to the first skin wound. In guinea pig no. 1 the coated catheters were inserted on the right side and uncoated controls on the left side. In guinea pig no. 2 the position of catheters was the opposite.

Both guinea pigs were anaesthetized and exsanguinated one week after surgery. The quantity of thrombus masses around the intravasal catheters and on the vein was recorded. The intramuscular catheters were removed and pieces of muscle tissue and subcutaneous tissue around the catheter canal were isolated and fixed for subsequent microscopy.

No signs of overt reaction to the catheters were observed during the week from surgery to sacrifice. The weight of the thrombus formations found at the front end of the catheter is as follows:

Guinea pig No.	Catheter	Thrombus weight (g)
1	Right (coated)	0.49
1	Left	1.71
2	Right	0.28
2	Left (coated)	0.05

In the subcutaneous tissue no reaction was seen around any of the catheter canals. In the muscle tissue from both the right and left side a very thin grayish zone was seen around the catheter canal. There was no difference in this respect between the right and left side. Microscopically a subcutaneous membrane rich in mononuclear cells and small vacuoles were found along the catheter canal, and in the surrounding connective tissue foreign body giant cells were seen. There were no significant differences in this regard between coated and control sites.

CLAIMS

1. Use of sucralfate for the preparation of a medicament for topical application to the skin or to any non-gastrointestinal, non-oral mucosal surface of an animal or a human, including the lining of body cavities, for the prophylaxis or treatment of any manifestation of inflammation or infection, for modification or facilitation of tissue regenerative processes, for the modulation of immune reactions, for the treatment or prophylaxis of non-bladder pre-malignant or malignant disorders, or for the prophylaxis or treatment of irritation, burns, or ulceration of the skin, connective tissue, or non-gastrointestinal, non-oral mucosa; or for the preparation of a medicament for topical application to the skin or any non-oral mucosal surface of an animal or a human for the treatment of laceration, lesions, or surgical wounds of the skin, connective tissue, or non-oral mucosa, or for the prophylaxis or treatment of skin, connective tissue, or non-oral mucosal aging.

2. Use according to claim 1, wherein the medicament is in a form suitable for topical application to the skin or mucosa, e.g. a powder, paste, ointment, lotion, gel, cream, salve, emulsion, suspension, spray, sponge, strip, plaster, pad, dressing or ostomy plate.

3. Use according to claim 1 or 2, wherein the medicament is in the form of a topical preparation comprising the sucralfate in an amount of 0.001-99%, typically 0.01-75%, more typically 0.1-20%, especially 1-10%, such as 2-6% by weight of the preparation.

4. Use according to any of claims 1-3, wherein the sucralfate is in the form of particles of a particle size of about 200 μm or less, such as 100 μm or less, e.g., 50 μm or less, such as 20 μm or less, e.g., 10 μm or less, such as about 1-5 μm or less.

5. Use according to any of claims 1-4, wherein the topical preparation is intended for application 1-10 times a day.

6. Use according to claim 1, wherein the mucosa are the vaginal, nasal or ocular mucosa.

7. Use according to claim 5, wherein the sucralfate is combined with a non-sulphated polysaccharide, for instance hyaluronic acid.

8. Use according to claim 6 or 7, wherein the medicament is in the form of a topical preparation comprising 0.1-99% by weight, preferably 1-75% by weight, more preferably 1-30% by weight of the sucralfate, calculated on the weight of the preparation.

9. Use according to claim 8, wherein the medicament is in the form of a topical preparation comprising 1-10% by weight of sucralfate, calculated on the weight of the preparation.

10. Use according to claim 8 or 9, wherein the medicament is in a form suitable for vaginal, nasal or ocular application such as a vaginal suppository, a tampon, a suspension for vaginal irrigation, a vaginal tablet or troche, a vaginal cream or gel or ointment, a nasal insert, a nasal drop or spray, a nasal ointment or gel, or eye drops, eye salve, eye gel, or an insert.

11. A pharmaceutical preparation, in particular for topical application to skin or any non-bladder, non-gastrointestinal, non-oral mucosal surface, which comprises sucralfate together with a pharmaceutically acceptable carrier or excipient.

12. A pharmaceutical preparation according to claim 11, which is designed for topical application to mucosas of the nose, respiratory tract, eye, ear, vagina, vulva, to borderline areas such as lips and perianal areas, and to the skin.

13. A pharmaceutical preparation according to claim 11 or 12 which is in the form of a powder, paste, ointment, lotion, gel, cream, salve, emulsion, suspension, spray, sponge, strip, plaster, pad, dressing or ostomy plate.

14. A pharmaceutical preparation according to any of claims 11-13 which contains the sucralfate in an amount of 0.001-99%, typically 0.01-75%, more typically 0.1-20%, especially 1-10% by weight of the preparation.

15. A pharmaceutical preparation according to any of claims 11-14 wherein the sucralfate is in the form of particles of a particle size of about 200 μm or less, such as 100 μm or less, e.g., 50 μm or less, such as 20 μm or less, e.g., 10 μm or less, such as about 1-5 μm or less.

16. A method for preventing or treating any manifestation of inflammation or infection of the skin or any non-gastrointestinal, non-oral mucosal surface of an animal or a human, including the lining of body cavities; for modifying or facilitating tissue regenerative processes; for modulating immune reactions; for preventing or treating non-bladder pre-malignant or malignant disorders; for preventing or treating irritation, burns, or ulceration of the skin, connective tissue, or non-gastrointestinal, non-oral mucosa; for the treatment of laceration, lesions, or surgical wounds of the skin, connective tissue, or non-oral mucosa; or for preventing or treating skin, connective tissue, or mucosal aging, the method comprising applying to the skin, mucosa or tissue a therapeutically or prophylactically effective amount of sucralfate.

17. A method according to claim 16, wherein the sucralfate is combined with a non-sulphated polysaccharide, for instance hyaluronic acid.

18. A method according to claim 16 or 17, wherein the sucralfate is applied as a powder, paste, ointment, lotion, gel, cream, salve, emulsion, suspension, spray, sponge, strip, plaster, pad, dressing or ostomy plate.

19. A method according to any of claims 16-18, wherein the sucralfate is applied 1-10 times a day.

INTERNATIONAL SEARCH REPORT

International Application No PCT/DK88/00216

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) *

According to International Patent Classification (IPC) or to both National Classification and IPC 4

A 61 K 31/70, 31/715

II. FIELDS SEARCHED

Minimum Documentation Searched 7

Classification System	Classification Symbols
IPC 4	A 61 K 31/70, 31/715, 31/72, 31/725, 31/735
US Cl	424:180, 183; 514:23, 25, 53-60

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched 8

SE, NO, DK, FI classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT 9

Category *	Citation of Document, 11 with indication, where appropriate, of the relevant passages 12	Relevant to Claim No. 13
X	EP, A, 230 023 (MARION LABORATORIES INC) 29 July 1987 See page 4, line 6 - page 16, line 16, examples 14-16. & JP, 62190127	1-3, 5-15
Y	EP, A, 136 100 (MARION LABORATORIES INC) 3 April 1985 See page 1, line 26 - page 4, line 2, example. & CA, 1218601 AU, 564201	1-15
Y	American Journal of Gastroenterology, Vol. 80, No. 3, 1985, W.S. Brooks Jr, "Sucralfate: Nonulcer uses", pages 206-209, see the whole document.	1-15
P, Y	Dialog Informational Services, file 155, medline 66-88, accession No. 06600426, M.J. van Emery et al, "Sucralfate inhibition of tumor cell implantation in the bladder", & J. Urol, July 1988, 140 (1), pages 188-90, see the whole document.	1-15

.../..

* Special categories of cited documents: 10

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
1989-03-29	1989 -03- 3
International Searching Authority	**Signature of Authorized Officer**
Swedish Patent Office	Niklas Forslund

Form PCT/ISA/210 (second sheet) (January 1988)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers 16-19 because they relate to subject matter not required to be searched by this Authority, namely:

Method for treating the human or animal body by surgery or therapy (see rule 39 (iv)).

2. [ ] Claim numbers ..... because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out specifically

3. [ ] Claim numbers ..... because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
Y	US, A, 4 668 665 (K. ISHHARA ET AL) 26 May 1987 & EP, 0107209 JP, 59078116	1-15